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Single Case

Extramammary Paget's Disease and Melanoma: 2 Cases of Double Cancers

Erika Lydrup[a] Jais Oliver Berg[a] Sofie Vetli Hjorth[b]
Lisbet Rosenkrantz Hølmich[a] Jørgen Lock-Andersen[a]
Annette Hougaard Chakera[a]

[a]Department of Plastic Surgery, Herlev-Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark; [b]Department of Pathology, Herlev-Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

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Abstract
Extramammary Paget's disease (EMPD) is a rare intraepidermal neoplastic disease. There is a well-known relationship between EMPD and underlying malignancy. However, only a few cases of EMPD and cutaneous melanoma have been reported previously. In this case report we present 2 cases of such double cancers: one as a collision tumor, the other at separate sites. We discuss the pathogenesis, treatment, and importance of a thorough clinical and radiological examination and review the literature.

Introduction

Extramammary Paget's disease (EMPD) is an uncommon intraepidermal neoplastic disease presenting as a pruritic and erythematous plaque in apocrine gland rich skin including the ear, vulva, scrotum, axillae, groin, and perianal region [1, 2]. A relationship between EMPD and underlying in situ or invasive neoplasms is well known [1, 2]. However, only a few cases

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Erika Lydrup
Department of Plastic Surgery
Herlev-Gentofte Hospital, Copenhagen University Hospital
Borgmester Ib Juuls Vej 5, DK–2730 Herlev (Denmark)
erikalydrup@hotmail.com

of cutaneous malignant melanoma (MM) and EMPD have been reported to date: as collision tumors [3–5], at separate sites simultaneously with primary MM [6], or with relapsing MM [7]. In this case report 2 cases of such double cancers are presented; one patient with a collision tumor, the other at separate sites.

Patient Cases

The first patient was a 69-year-old woman, diagnosed 2 years earlier with superficial spreading MM on the left arm (1.1-mm Breslow thickness, with mitoses ≥1/mm^2, but no ulceration/regression, clinical stage IB). She was treated with wide local excision with a 2-cm margin and sentinel node biopsy from the left axilla without metastases. Postoperative follow-up was uneventful until 2 years later the patient noticed an itching rash in the perineal area. It was described as a large eczematous lesion of 3–4 cm on the left side of the perianal skin, covering about one third of the anal circumference without deeper infiltration. A biopsy showed EMPD. Gynecological examination and transrectal ultrasound were normal. The lesion was surgically removed with a 1-cm margin and the defect reconstructed with a local flap. PET-CT demonstrated a single FDG-positive lymph node in the left axilla, with no other suspicious foci. Ultrasound guided biopsy showed metastasis of MM. Left radical axillary lymph node dissection was performed and showed metastases in one of 27 lymph nodes without perinodal growth. The patient is being followed in a program for patients with a high risk of relapse, which consists of clinical follow-up every 3 months at the Department of Plastic Surgery and routine PET-CT scans at 6, 12, 24, and 36 months or sooner, if indicated. In addition to this, clinical follow-up and anoscopy is performed every 6 months for 2 years at the Department of General Surgery. A colonoscopy performed 3 months postoperatively was normal, and at 15 months of follow-up the patient was free from relapse (Fig. 1).

The second patient was an 86-year-old man, disabled due to sequelae after a stroke, and with a history of prostate cancer and multiple basal cell carcinomas. The patient presented with a large lesion behind and under the left ear. Two years earlier a biopsy had shown actinic keratosis (unclassified type), and the lesion was treated with imiquimod cream. Due to the growth of the lesion a new biopsy was taken showing MM, unknown whether it was a primary tumor or a metastasis. PET-CT was without sign of cancer elsewhere. The patient underwent wide local excision of the lesion with a 1-cm margin, and the histopathological examination showed unclassified MM with an abundance of spindle cells (a lentigo maligna MM was considered, but the lesion did not fulfill the criteria) and EMPD in the same area and incomplete margins. Upon revision, EMPD was shown to have been present in all specimens from the tumor area. The patient was unfit for major surgery in general anesthesia and rejected radiotherapy. Due to local relapse 9 months later of both MM and EPMD, the patient accepted palliative radiotherapy. Surveillance consists of clinical follow-up (Fig. 2, 3).

Discussion

James Paget was, in 1874, the first to describe a relationship between mammary Paget (MP) and underlying mammary carcinoma, and in 1889 H.R. Crocker was the first to describe EMPD of the scrotum and penis [1]. In women, the vulva is the most common location for EMPD, followed by the perianal region [1, 2]. It usually affects individuals aged 50–80 years and is most frequently seen in Caucasian women [2, 8].

Around 70% of patients present with pruritis, which is the most common symptom [2]. Because of its nonspecific presentation, EMPD is often misdiagnosed as an inflammatory or infective skin condition (i.e., eczema, seborrheic dermatitis, or psoriasis), as described in our second case, and it is therefore not uncommon for the lesion to be advanced before correct diagnosis is established and appropriate treatment initiated [1].

The current theory is that EMPD in most cases arises as a primary intraepidermal neoplasm (primary EMPD), and less commonly as a result of spread from an underlying internal malignancy (secondary EMPD). Primary EMPD may progress to dermally invasive adenocarcinoma, and if not treated, may metastasize to local lymph nodes and distant sites. Conversely, secondary EMPD arises from epidermotropic spread of malignant cells from an underlying neoplasm [1, 2].

Some associate EMPD with a generalized tendency to neoplasia, especially adenocarcinoma. Vulval EMPD has been associated with neoplasm in the endometrium, endocervix, vagina, vulva, urethra, and bladder, while EMPD on the external male genitalia may be associated with neoplasms arising in the bladder, urethra, and prostate. On average, 25% of EMPD cases are thought to be associated with other neoplastic diseases, though the frequency varies with the site of the disease [1]. Among vulval EMPD, 11–20% are associated with underlying visceral malignancy [9, 10]. Perianal EMPD is rarer than vulval EMPD but is strongly associated with adenocarcinoma of the anus and colorectum in 14–45% [1, 11, 12]. In most cases the correct diagnosis can be reached with careful morphological evaluation and help of a panel of immunohistological markers. The most common differential diagnoses are melanoma and atypical squamous disease.

There is a high rate of local recurrence, which might be due to the clinical features of EMPD, namely irregular margins, multicentricity, and the tendency to involve apparently normal skin, which can make radical resection difficult [2]. One study [10] based on 100 cases found a recurrence rate of 34%, at a median of 3 years. Another study [13] with 30 cases reported a recurrence rate of 44%, and patients with invasive disease had higher rates of local recurrence than those with in situ disease.

The standard treatment of EMPD is wide local excision with at least a 1-cm margin [1]. To enhance the chance of clear margins, immunohistochemistry should be used in the pathological examination, and if necessary supplementary cuts of the tissue specimen should be performed. It is also possible to perform frozen sections.

Due to the high frequency of associated cancers, diagnosis of EMPD should be accompanied by a thorough investigation, which may include colonoscopy, sigmoidoscopy, chest X-ray, or PET-CT. Follow-up of patients diagnosed with EMPD is necessary and needs to continue long term. It should address both the risk of local recurrence and associated internal malignancies [2].

To our knowledge, a history of both EMPD and MM has only been reported 5 times to date [3–7]. EMPD and relapsing MM is extremely rare, and we only found 1 case reported [7]. There is sparse literature describing a relationship between EMPD and MM and still no evidence for an existence of such. Tsuji et al. [6] discussed this and suggested that different underlying genetic mechanisms for EMPD and melanoma could explain a general lack of association.

In this case report we present 2 different cases with MM and EMPD. Our first case describes relapsing MM and EMPD and demonstrates that PET-CT scan is a valuable tool in the investigation when a patient is diagnosed with EMPD. Our second case with a collision tumor of MM and EMPD presents two issues. Firstly, EMPD is often misdiagnosed, delaying the diagnosis. Secondly, meticulous pathological examination of the specimen is important due to multifocality of the lesion. It is possible that our cases just represent two coincidences. However,

we wish to highlight the likelihood of a relationship between EMPD and MM and recommend a full-body skin examination as part of the clinical examination of all patients diagnosed with EMPD, as it may be associated with MM. PET-CT scans have limited capability to show small cancers of the skin.

Statement of Ethics

The authors have no ethical conflicts to disclose. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients gave their written informed consent, including for the use of the photograph.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

All authors made substantial contribution to all of the following: (1) conception and design of the work, (2) drafting the work or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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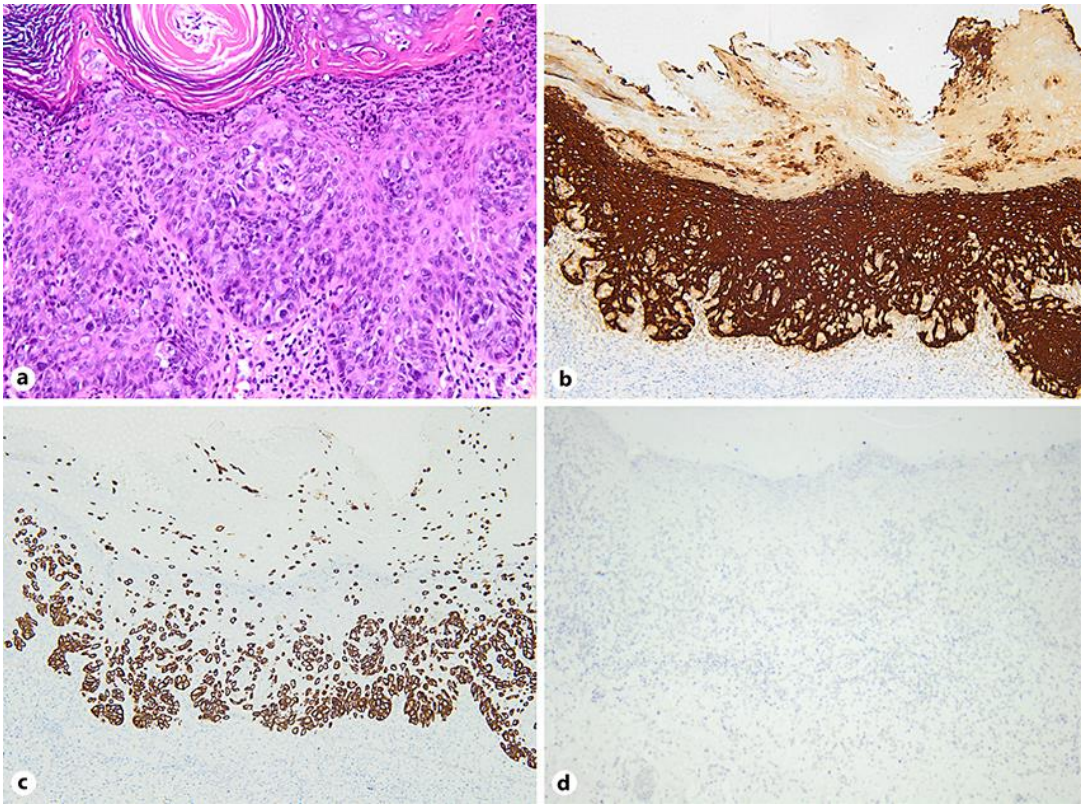

Fig. 1. **a–d** Histological presentation of the perianal skin showing Paget cells located in the epidermis. **a** Neoplastic cells with abundant cytoplasm and large vesicular nuclei with prominent nucleoli are arranged in confluent nests and as single cells throughout the epidermis. Hematoxylin-eosin. ×20. Tumor cells were negative for CK5 (**b**), but the cells stained for CK7 (**c**). **d** Tumor cells express Ber-EP4, allowing the diagnosis of extramammary Paget disease. Immunohistological staining. Magnification, ×10. The cells were negative for Sox10 (immunohistological stain).

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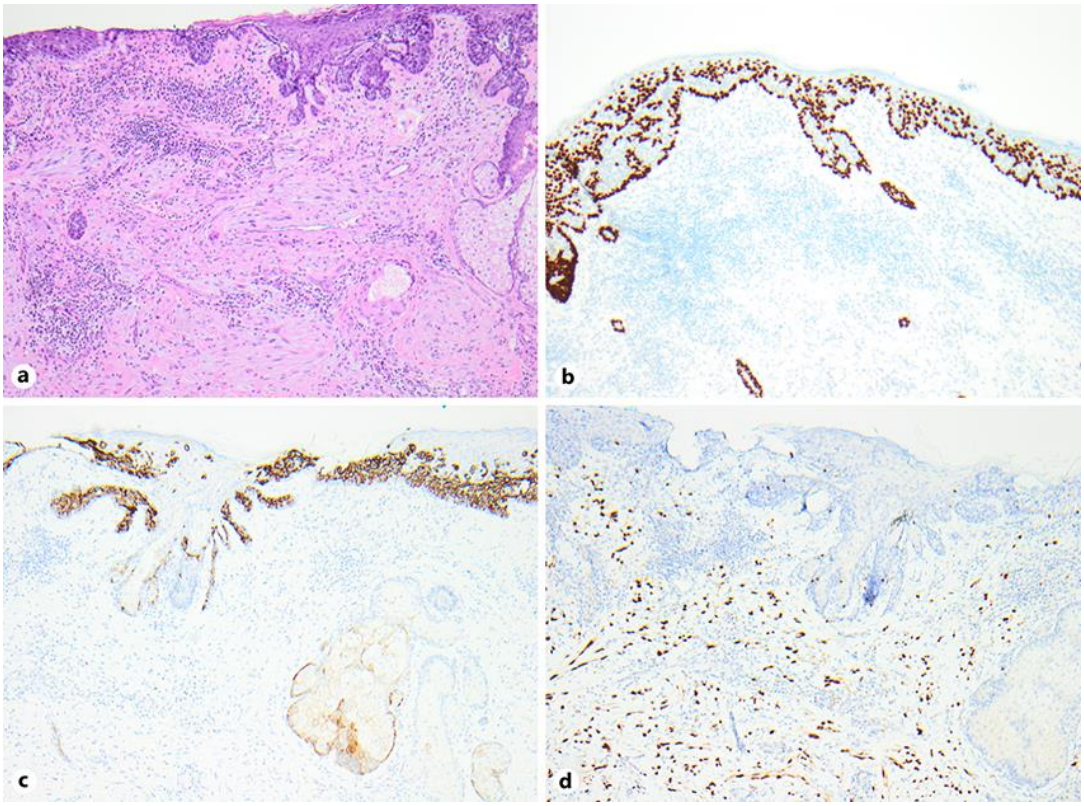

Fig. 2. Histological presentation of postauricular skin next to the melanoma. Paget cells are located in the epidermis and in the adnexal epithelium in the dermis. **a** Pagetoid distribution of Paget cells in the epidermis. Hematoxylin-eosin. ×20. **b** Tumor cells were negative for P40, while normal epithelium was positive. **c** Cells stained for CK7. Immunohistological stains. Magnification, ×10. **d** Sox10 staining of invasive melanoma. Immunohistological stain. Magnification, ×10. Immunohistological stains: CK7, cytokeratin 7; P40, protein 40; Ber-EP4, epithelial cell adhesion molecule; Sox10, Sox10 protein.

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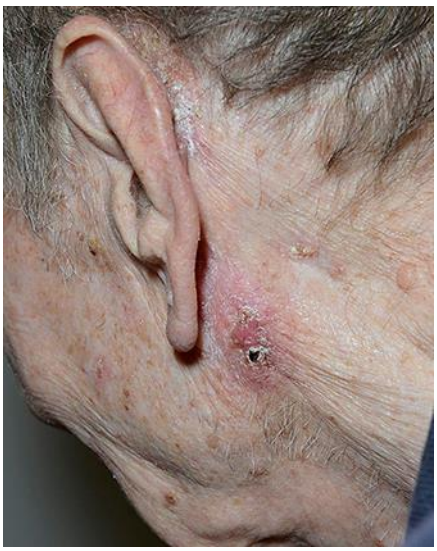

Fig. 3. Clinical photograph of the lesion behind the left ear. Biopsy showed MM and EMPD in the same area.